ALMAC

Quality Considerations & Role of Qualified Person (QP) & Responsible Person (RP)

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Agenda

EU Legislation

Licensing Terminology

Key Quality Milestones

- Pre-submission
- Post-submission

Key Messages

NI – Current Position

Jan 2020 UK withdrawal from the European Union

- **Withdrawal Agreement (2020)**
  - Article 7 confirmed the continued EU acceptance of testing and QP certification of batches imported into, and manufactured in, Northern Ireland – **Unique Regulatory position for NI.**
- **EU-UK Trade and Cooperation Agreement (2021)**
  - Dedicated annex on medicinal products
  - Recognition of inspections and GMP documents (certificates) & agreement on conformity of GMP standards
- **Northern Ireland Protocol (2021)**
  - Ensures ongoing regulatory alignment with EU and free movement of goods between EU and NI

NI – Current Position

- **Windsor Framework (effective 01 Jan 2025)** sets out a long-term solution for the supply of medicines into Northern Ireland
  - New medicines for the UK market will be authorised by UK authorities, and UK packaging must carry a clearly legible ‘UK only’ label to be allowed onto the UK market, including in Northern Ireland
  - These products will only be able to be sold in the UK, and will not be available on the market in the EU
  - Medicines entering Northern Ireland will not display features required under the EU Falsified Medicines Directive (FMD) including 2D barcodes and serialisation numbers that are compliant with the EU FMD Directive
  - The MHRA will expect anti-tamper devices to remain on all medicine packaging.

NI – Current Position

- **NI Protocol**
  - **Part of a legally binding international treaty**
  - **Remains in full force and effect**
- **In absence of NI Protocol**
  - **Withdrawal agreement remains in force, unique regulatory position (testing and QP certification of batches imported/manufactured in NI, accepted by EU)**
- **QP Certification for EU supply can be performed by a QP named on the CR (UK) MIA and ROI (EU) MIA.**

EU Legislation

- Regulations
- Directives
- Decisions
- Recommendations / opinions / guidelines

Guidance for the interpretation of EU GMPs is described in the Eudralex Volume 4 – "*The Rules governing Medicinal Product in the EU*"

Licensing Terminology

Marketing Authorisation Holder (MAH)

- The company who has been granted the marketing authorisation
- Need to establish an EU entity as MAH and be able to procure, supply and export product under a WDA to get product to patient.
- Final milestone in product launch in your supply chain after Almac QP responsibilities

Marketing Authorisation (MA) (Product Licence)

- A marketing authorisation lays down the terms under which a medicinal product is authorised to be marketed in the EU
- Follows the ICH CTD format
- Contains authorised DS and DP manufacturing and testing sites
- Module 3 Quality

Licensing Terminology

Manufacturing and Importation Authorisation (Site Licence)

- EU pharmaceutical companies hold a Manufacturers' Importers Authorisation (MIA), which is essentially a "site license"
- MIA details the manufacturing and packaging activities that a company is authorised to carry out, and also lists the personnel that are authorized to act as a Qualified Person at the site
- Almac Pharma Services hold a MIA at both our CR and DK facilities

Wholesale Distribution Authorisation (Site Licence)

- Requires an EU **Responsible Person** to be named on the WDA, clearly defined roles and responsibilities for the RP
- Issued by the local Regulatory Authority
- Comply with GDP, inspected prior to issuance of WDA
- Periodically inspected against **Good Distribution Practice of Medicinal Products for Human Use (2013/C 343/01)**

Key Quality Milestones

Pre-submission

1. Establish QP Certification Site

2. Quality Technical Agreements / QP to QP agreements
3. QP Declaration

Post-submission

4. Initiate Final Quality Technical Agreement
5. Release Testing and EU Import Testing
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8. Marketing Authorisation Approval
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1 – Establish QP Certification Site

- Certification by a Qualified Person is required by law to release your product for sale within the EU.

- The Qualified Person - responsible for ensuring that each batch has been manufactured and checked in accordance with:
  - Laws in force in the Member State where certification takes place
  - The requirements of the marketing authorisation (MA)
  - Good Manufacturing Practice (GMP)

  and is permitted under the terms of the MIA

- The ultimate responsibility for the performance of a medicinal product over its lifetime, its safety, quality and efficacy lies with the Marketing Authorisation Holder.

Requirement for the QP

- Legal requirement in EU directives
  2001/83/EC ‘Medicinal Products For Human Use’
- QP bound under a code of conduct
- Technical, ethical and professional obligations in terms of assuring quality, safety and efficacy of a batch of medicinal product
- Point of contact for supervisory authorities such as MHRA, HPRA (or EMA) in case of product investigations
- Each MIA holder is required to have at least one QP at their disposal

Responsibilities - QP

Eudralex Volume 4, Annex 16 ‘Certification By A Qualified Person And Batch Release’ details that the Qualified Person (QP) must ensure:

- Certification is permitted under the terms of the MIA
- Any additional duties and requirements of national legislation are complied with
- Certification is recorded in a register

Delegate:

- Defined Supply Chain Map
- Audits of manufacturing and testing sites
- Compliance with registered specification
- FMD compliance

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2 –Quality Technical Agreements

- Written contractual agreement describing respective responsibilities between MAH and contract acceptors with regards to GMP activities.
- GMP requirement
- Initially required to underpin the responsibilities for providing the QP Declaration.
- If more than one MIAH in supply chain within the EU a QP to QP agreement should be established.

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3– QP Declaration

Marketing Authorisations must only use Active Pharmaceutical Ingredients (APIs), which have been manufactured in compliance with EU GMP

- Compliance with this requirement is confirmed by a “QP Declaration”, which is submitted with the MAA
- GMP compliance confirmed through audit
- Template QP declaration has been issued by the European Medicines Agency (EMA).

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PART A: Concerned active substance manufacturing sites

Name of Active Substance:

Name and Address of Active Substance Manufacturing Site[1,2]	**Manufacturing Operation / Activity[3]**

1. List each site involved in the synthesis of the active substance beginning with the introduction of the designated active substance starting material, include intermediate manufacturing sites / part–processing sites.

2. State the site name and address in detail, including the building numbers (if applicable).

3. For example – Full or partial manufacture of the active substance, micronisation.

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PART B: Manufacturing / Importer Authorisation Holder(s) (MIAHs) to which this QP declaration applies

This QP declaration is applicable to the following registered MIAH(s), that use the active substance as a starting material and/or is responsible for QP certification of the finished batch of a human or veterinary medicinal product, where the active substance is registered as a starting material and is manufactured at the sites listed in Part A:

MIAH Site	**MIAH Number**	**Manufacturing Activity**

PART C: Basis of QP Declaration of GMP Compliance

Please tick section (i), complete the table in section (ii) and, if applicable, add the supplementary supporting information to section (iii).

(i) ☐ On-site audit of the active substance manufacturer(s)

(ii) Audit(s) of the active substance manufactured at the site(s) listed in PART A has/have been completed either by the MIAH(s) listed below or by a third party auditing body(ies) i.e. contract acceptor(s) on behalf of the MIAHs i.e. contract giver(s) as listed:

MIAH Site (or contract giver)	Auditing body (contract acceptor)	Site audited	Date of audit[4]

4 Justification should be provided if the date of last audit exceeds 3 years:

PART D: QP declaration of GMP compliance

I declare that:

QP Responsibility

- I am a QP with specific responsibility for GMP compliance of the active substance manufactured at the sites listed in Part A and I am authorised to make this declaration.
- The audit report(s) and all the other documentation relating to this declaration of GMP compliance of the active substance manufacturer(s) will be made available for inspection by the competent authorities, if requested.

GMP Compliance

- The manufacture of the named active substance at sites given in Part A is in accordance with the detailed guideline on good manufacturing practice for active substances used as starting materials as required by Article 46(f) of Directive 2001/83/EC and Article 50(f) of Directive 2001/82/EC.
- This is based upon an audit of the active substance manufacturer(s).
- The outcome of the audit confirms that the manufacturing complies with the principles and guidelines of good manufacturing practice.

Audit

- In the case of third party audit(s), I have evaluated each of the named contract acceptor(s) given in Part C and that technical contractual arrangements are in place and that any measures taken by the contract giver(s) are documented e.g. signed undertakings by the auditor(s).
- In all cases, the audit(s) was/were conducted by properly qualified and trained staff, in accordance with approved procedures.

Responsibilities in the case of multiple MIAH(s):

- This declaration is made on behalf of all the involved QPs named on the relevant MIAH(s) specified in Part B;

A documented procedure defining GMP responsibilities is in place and that technical agreements exist between the named companies concerning management of GMP responsibilities.

QP Declaration for APIs

Summary of the QP Declaration requirements:

1. Quality agreement in place detailing responsibilities
2. Establish the supply chain
3. Sites involved in manufacture of the API listed by name, address & function
4. Sites involved in DP manufacture are listed by name, address & manufacturing activity
5. Audits of sites involved in API manufacture have been completed within the last 3 years.

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4– Quality Technical Agreement

- Initiate update to QTA to cover full scope of manufacturing and testing activities and PQS expectations.
- Allow plenty of time to establish.
- Must be approved by parties.
  - Prior to receipt of bulk DP
  - Prior to 1st launch batch
  - Prior to manufacturing activities

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5– Release / EU Import Testing

Understand your supply chain

- Identify of the site of import into the EU (if applicable)
- Mutual Recognition Agreements (MRAs) between the EU and;
  - Canada
  - Japan
  - Australia
  - New Zealand
  - Switzerland
  - Israel
  - USA
- Brexit

Release / Import Testing

Completion of the release testing and import testing sites must be listed in the MA

- Testing is performed as per the MA specification
- Each batch must be sampled within the EU unless it can be technically justified and documented to sample in the 3rd country
- Reference and retention samples

Testing Methods

- Implementation of all release test methods at EU-based analytical laboratories (physical, chemical and biological)
- Initiate with method familiarisation (theoretical and practical)
- Formal method transfer and/or validation (chemistry/ microbiological)
- If QP certification site is different to testing sites oversight by the QP will need to established including the communication of OOS.

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6 - Audits

- Each manufacturing, packaging, release testing site listed in MA to be audited to EU GMPs.
  - MAH audit report
  - 3rd Party report
  - QP or QP delegate
- Reports should be sufficiently detailed for assessment to be made.
- Risk based approach considering; location of site (EU/3rd Country), dosage form, regulatory history.

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7- Product Launch Readiness

Compile the information which will be relevant to Batch Certification by the QP

- Typically based on a “final draft MAA” and confirmed/finalised when approved
- Supply Chain ‘Map’ of active Substance and Medicinal Product up to the point of certification
- Third party manufacturing records reviewed.
- Compilation of product-specific checklists

Product Launch Readiness

- Establish batch numbering rules
- Expiry date formats
- Establish mechanisms for:
  - Ensuring Almac QP has access to the MA and any variations – management of changes
  - Dealing with routine product quality issues
  - Routine sharing of manufacturing records

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8 – Marketing Authorisation approval

- Provide a final approved MA to the certification site; gap analysis for any changes from final draft
- Post approval commitments understood
- Supply Chain Map finalised
- Shipping qualifications closed
- Packaging validations closed (inc serialisation)

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9- QP Certification

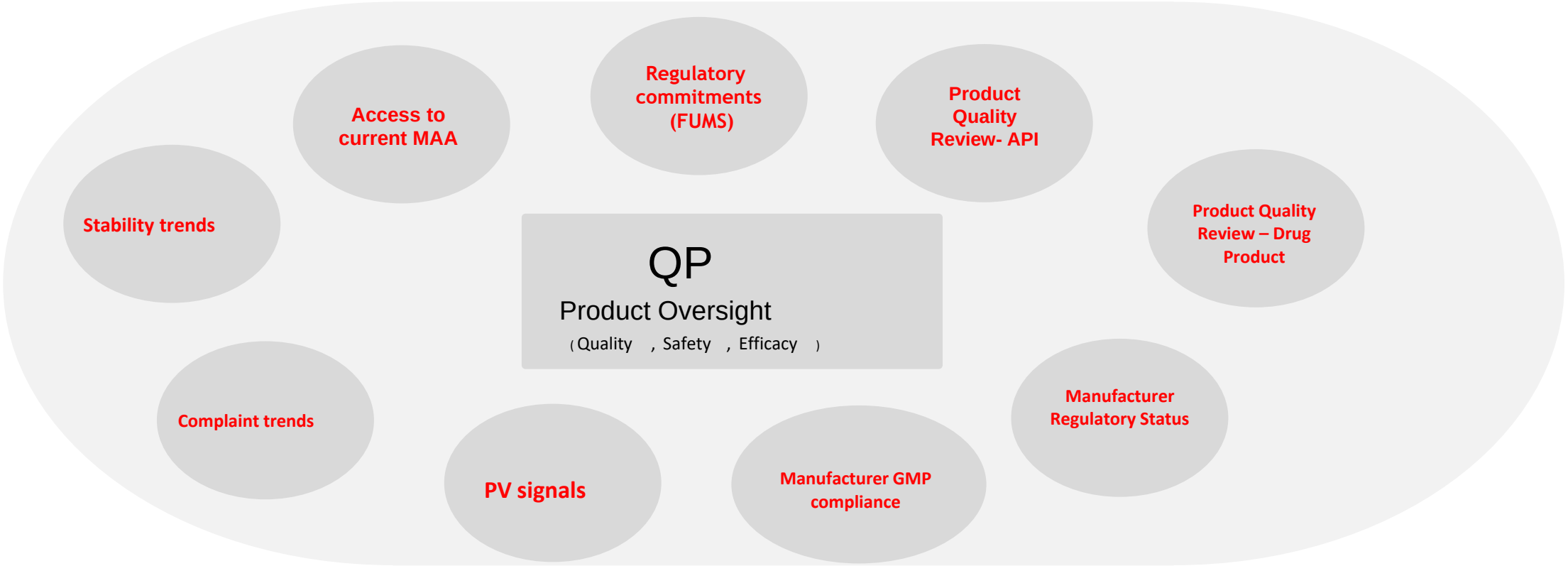
Can involve extensive reviews of:

- Manufacturing & packing batch records for compliance with and EU GMP
- Partial Manufacturing Certification from 3rd party sites (EU S
- Deviations, OOS results or environmental failures from drug product sites
- Release test results from EU import testing
- Temperature conditions during shipment to EU site

Required to certify Batch Certification is confirmation of compliance the

- Marketing Authorisation
- EU GMP
- Quality Agreement

QP Oversight



RP Oversight

Key Messages/Common Pitfalls

Plan key activities well in advance of target product launch date to meet milestones:

- QP Declaration rejected at validation stage by EMA - details not aligned with registered details in the MA
- Insufficient time/consideration for WDA (allow at least 6 months)
- CMOs not willing to share full audit reports/observations with the QP – plan for CDAs if required
- Not defining/understanding the entire supply chain, e.g storage sites which will not be listed in the MA
- Insufficient time for planning audits by suitably qualified personnel
- Not defining shared QP responsibilities properly
- Sharing quality critical information and current MA – make sure access is arranged for all parties
- No process to manage batch record review queries at third party sites

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Questions